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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1644	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,126	GOODWIN ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-30,32-45 and 50-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,32-45 and 50-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments, filed 3/21/2002 and 1/8/2002 (Paper Nos. 10 and 8, respectively), are acknowledged.

Claims 27-30, 32-45, and 50-69 are pending.

Applicant's election without traverse of Group II (claims 27-30, 32-39, 40-46, now claims 27-30, 32-45 and 50-69) in Paper No. 8 is acknowledged.

Applicant further elected a species of SEQ ID NO: 23 as a CD30L polypeptide and calicheamycin as a therapeutic agent. Upon further consideration, the search has been extended to include SEQ ID NOS: 6, 8, and 19 and all of the therapeutic agents as recited in claims 50-66

Claims 27-30, 32-45, and 50-69 are under consideration in the instant application.

2. Applicant should amend the first line of the specification (37 CFR 1.78) to update the status of allowed U.S. application 09/079,785.

3. Applicant's IDS, filed 1/3/2002 (Paper No. 7), is acknowledged, however, the Dallenbach et al. and Stein et al. citations crossed out were not found in the priority documents. The Pfreundschuh et al. citation was crossed out because a translation was not provided. Applicant is invited to produce such documents.

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The instant specification lacks antecedent basis for the method step as recited in original claim 29 (i.e. wherein the conjugate is administered in an effective amount to a human afflicted with said malignant cells).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

In the present instance, claim 62 recites a Markush Group including saporin toxin, ribosomal inactivating proteins, and mycotoxin. Mycotoxin and saporin toxin are ribosomal inactivating proteins, therefore, the ribosomal inactivating proteins are the broad recitation and mycotoxin and saporin toxin are the narrower limitations. It is noted that mycotoxin is already recited in dependent claim 63. Applicant can overcome this rejection by deleting mycotoxin and saporin toxin from claim 62 and reciting saporin in a dependent claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 27-30, 32-45, and 50-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a therapeutic agent to CD30+ cells comprising administering a soluble CD30L consisting of SEQ ID NO: 19 or 23 conjugated to one or more therapeutic agents to a human afflicted with CD30+ malignant cells (i.e. cancer), does not reasonably provide enablement for a method of delivering a therapeutic agent to CD30+ cells comprising administering any full-length CD30L polypeptide, any other soluble fragment of CD30L, or fragments of extracellular or cyotsolic domain fragments of any full-length CD30L polypeptide conjugated to one or more therapeutic agents to a human afflicted with any other type of disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the polypeptide of sequences of SEQ ID NOS: 19 and 23, the specification fails to provide guidance as to how to make conjugates of full-length CD30L (membrane-bound protein on a cell surface) with a therapeutic agent attached for administration of cells to a subject for cancer therapy.

The genus encompasses "fragments" wherein such fragments have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes. The specification fails to provide guidance how to make a fragment of the CD30L comprising the transmembrane and cytoplasmic domains of SEQ ID NOS: 6 and 8 which is encompassed by claims 27-30, 32(e), 33-34, 36-46, and 50-68 and 69(e). Only fragments that are enabled are SEQ ID NOS: 19 and 23, comprising the extracellular region of mouse and human CD30L, respectively. The specification fails to provide guidance how to make a fragment of a fragment as recited in claims 32(e), 35, and 69(e). One skilled in the art would not know how little or which amino acid sequences are essential for binding to CD30. "Comprising" is considered "open" language and includes amino acid sequences outside of the disclosed extracellular domains consisting of SEQ ID NOS: 19 and 21. Applicant has not enabled one skilled in the art for the genus of

CD30L polypeptides and fragments thereof. Applicant has taught human and murine CD30L, and extracellular domains of human and murine CD30L. The sequences have differences in amino acid content, therefore, applicant has not taught the genus of CD30L polypeptides and fragments thereof (mammalian or otherwise).

However, the present specification fails to provide sufficient disclosure of such "fragments" that maintain the structural and functional properties of the CD30L polypeptide and extracellular domains set forth in SEQ ID NOS: 19 and 23 wherein the other amino acids can vary. The specification does not provide sufficient guidance as to which of the amino acids may be changed while CD30L structural or functional activity and specificity is retained. Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated amino acids consisting of "a fragment of a fragment" encompassed by the claimed invention other than "amino acids set forth by SEQ ID NOS: 19 and 23" would be expected to have greater differences in their activities.

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which

structures would lead to functional CD30L polypeptides or fragments thereof with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 27-30, 32-45, and 50-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of delivering a therapeutic agent to CD30+ cells comprising administering a soluble CD30L consisting of SEQ ID NO: 19 or 23 conjugated to one or more therapeutic agents to a human afflicted with CD30+ malignant cells (i.e. cancer).

Applicant is not in possession of a method of delivering a therapeutic agent to CD30+ cells comprising administering any full-length CD30L polypeptide, any other soluble fragment of CD30L, or fragments of fragments of any full-length CD30L polypeptide conjugated to one or more therapeutic agents to a human afflicted with any other type of disease.

The specification fails to define all functional fragments or even fragments of the extracellular domains (i.e. fragments). The lack of sufficient limitations would therefore allow for a wide range of fragments in the

absence of defined structure. Therefore, the skilled artisan cannot envision all of the contemplated "fragments" recited in the instant claims. A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. See Fiers, 984 F.2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g. structural feature), is not a description of that material. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993). A description of a genus of "fragments" may be achieved by means of a recitation of a representative number of sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Filing Date of the Instant Claims

8. For purposes of the prior art rejection, the filing date of the instant claims is deemed to be 04/12/1994, that of parent application 08/225,989. Parent applications 07/966,775, 07/907,224, 07/899,660, 07/892,459, and 07/889,717 provide support for the use of CD30L as a research tool to study pathogenesis, in vitro assays for detection of CD30 or interactions with CD30, for purification of CD30, CD30L fusion proteins to facilitate purification and identification of CD30L and for a binding assay to detect cells expressing CD30L; but do not provide sufficient support for the instant claims wherein the full-length protein or extracellular domain of CD30L is conjugated to a therapeutic agent, such as those recited in instant claims 27-30, 32-45, and 50-69 for delivering said therapeutic agent to $CD30^+$ cells in vitro or to $CD30^+$ cells in a patient.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27, 38, 50, and 61-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Patent 5,165,923 (IDS reference) and the known fact disclosed in the specification on page 4, lines 12-13.

The '923 patent teaches a method of delivering a therapeutic agent to CD30+ cells comprising contacting said cells with a conjugate comprising toxins (i.e. therapeutic agents) such as ricin, diptheria, abrin, Pseudomonas exotoxin A, and ribosomal inactivating proteins, such as saporin as the toxins attached (i.e. disulfide bonds) to an anti-CD30 antibody for the treatment of Hodgkin's disease and lymphomas associated with CD30+ lymphocytes (see the Abstract, column 1, paragraph 4; column 2, paragraphs 1-2; column 7, paragraphs 2-3 and 5; column 8, paragraph 2; and claims 1, 11-13, 17-19, and 23-24 in particular). The '923 patent teaches that there is a need for new agents for the management of or

treatment of Hodgkin's disease that are free from mutagenic side effects, such as toxins conjugated to antibodies directed against Hodgkin cell associated antigens (i.e. CD30; see column 1, paragraphs 2-3 in particular).

The specification discloses on page 4, lines 12-13 defines "CD30L" as "the genus of polypeptides which are capable of binding CD30. A CD30-specific antibody inherently is a polypeptide which is capable of binding CD30.

Therefore, the '923 patent anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 27, 38, 50, 58-63, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762.

The '923 patent has been discussed supra.

The '923 patent does not teach using the natural CD30L as the targeting molecule.

WO 92/00762 teaches the use of targeting toxins to receptors via the use of antibodies or fragments thereof directed to the receptor, or the use of the natural ligand for the receptor, or a functional fragment or derivative thereof which can be coupled to the toxin for treatment of tumor cells (see page 2, paragraphs 4-5; and page 1, paragraphs 2-3 in particular). The toxin can be Pseudomonas exotoxin, calicheamicins, mycotoxin, and radionuclides (see page 3, paragraph 6 page 5, paragraphs 6-7; page 6, lines 1-2) which may be coupled to the natural ligand in any suitable way, such as a linking molecule and/or a spacers (see page 6, paragraphs 1-2 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the natural ligand as taught by WO 92/00762 for CD30 for the antibody directed against CD30 taught by the '923 patent to create a specific immunotoxin for Hodgkin's disease and lymphomas using the natural CD30L as the targeting molecule.

One of ordinary skill in the art would have been motivated to substitute the natural ligand taught by the WO 92/00762 document for the anti-CD30 antibody taught by '923 patent because both targeting moieties are directed to CD30 molecules present of the cell surfaces of Hodgkin's disease and lymphoma tumor cells, and therefore, are polypeptide equivalents. When conjugated to the toxic moieties taught by both the '923 patent and the WO 92/00762 document, both are effective as cancer therapies that are free from mutagenic side effects of radiation.

10. Claims 51, 54-57, 59, 62, 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63, and 65 above, and further in view of U.S. Patent 5,541,287.

The '923 and WO 92/00762 references have been discussed supra.

The combined reference teachings do not teach the use of vinblastine (instant claim 57), doxorubicin (instant claim 59), bleomycin (instant claim 59), 5-fluorouracil (instant claim 55), cyclophosphamide (instant claim 51), trichothecene (instant claim 64) or a radionuclide, such as ^{131}I, ^{211}AT, ^{77}Br, ^{186}Re, ^{188}Re, ^{212}Pb, ^{212}Bi, ^{109}Pd, ^{64}Cu, and ^{67}Cu (instant claim 66), as the specific therapeutic agent.

The '287 patent teaches methods, compounds, and compositions useful for delivering a targeting moiety (i.e. therapeutic agent) that is conjugated to one member of a ligand/anti-ligand pair to a patient for cancer therapy (see column 1, paragraphs 2 and 4; and column 5, paragraph 1 in particular) wherein the targeting moiety can be ricin (**instant claim 62**), Pseudomonas exotoxin A (**instant claim 62**), diptheria toxin (**instant claim 62**), saporin (**instant claim 62**), ribosomal inactivating proteins (**instant claim 62**), vinblastine(**instant claim 57**), doxorubicin (**instant claim 59**), bleomycin (**instant claim 59**), 5-fluorouracil (claim 55), cyclophosphamide (**instant claim 51**), trichothecene (**instant claim 64**; see column 8, paragraphs 1-4, in particular) or a radionuclide, such as ^{131}I, ^{211}AT, ^{77}Br, ^{186}Re, ^{188}Re, ^{212}Pb, ^{212}Bi, ^{109}Pd, ^{64}Cu, and ^{67}Cu (**instant claim 66**; see column 8, paragraphs 1-4; column 9, lines 55-63; and column 10, lines 1-3, in particular). The '287 patent teaches that the anti-ligand is preferably large enough to avoid rapid renal clearance and contains sufficient multivalency to accomplish cross-linking and aggregation or targeting moiety-ligand conjugates. Univalent anti-ligands are also contemplated. It is well within the purview of one of ordinary skill in the art to determine whether the best mode of the conjugate is univalent, a dimmer, a trimer, or a larger aggregate (see column 3, paragraph 1 in particular). Finally, the '287 patent teaches the invention overcomes problems with cancer therapy at that time, mainly that the method improved targeting ratio and increased the absolute dose to the target cell sites in comparison to conventional therapy (see column 1, paragraphs 3-4 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the specific targeting moieties (i.e. toxin) taught by the '287 patents for the therapeutic agents taught by the '923 and WO 92/00762 references because all of the conjugates are effective for cancer therapy of patients.

One of ordinary skill in the art would have been motivated to create said immunotoxin because the antibodies and therapeutic agents improved targeting ratio and increased the absolute dose to the target cell sites in comparison to conventional therapy, as taught by the '287 patent, such as Hodgkin's and lymphoma tumor cells as taught by the WO 92/00762 reference.

11. Claims 56, 57, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63, and 65 above, and further in view of U.S. patent 5,208,020.

The '923 and WO 92/00762 references have been discussed supra.

The combined reference teachings do not teach using cytotoxic agents such as daunorubicin (instant claim 59), doxorubicin (instant claim 59), vincristine (instant claim 57), and vinblastine (instant claim 57) as the specific therapeutic agent (instant claims 56-57 and 59-60).

The '020 patent teaches a method of delivering a conjugate comprising a therapeutic agent and maytansinoids or antibodies to selectively kill a specific cell population, such as tumor cells (see the Abstract, columns 1-2 in particular). The cytotoxic agents comprise daunorubicin, doxorubicin, vincristine, vinblastine, and calicheamycin (see columns 1-2 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cytotoxic agents taught by the '020 patent for the toxins taught by the '923 and WO 92/00762 references to create an effective immunotoxin to target CD30+ tumor cells.

One of ordinary skill in the art would have been motivated to create said immunotoxin because the antibodies and therapeutic agents selectively kill a specific cell population, as taught by the '020 patent, such as Hodgkin's and lymphoma tumor cells as taught by the WO 92/00762 reference.

12. Claims 50-51, 56-59, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63, and 65 above, and further in view of U.S. Patent 5,019,368.

The '923 and WO 92/00762 references have been discussed supra.

The combined reference teachings do not teach bleomycin (instant claim 59), cyclphosphamide (instant claim 51), dacarbazine (instant claim 50), daunorubicin (instant claim 59), doxorubicin (instant claim 59), 5-fluorouracil (instant claim 55), mechlorethamine (instant claim 50), procarbazine hydrochloride (instant claim 50), vinblastine (instant claim 57), vincristine (instant claim 57), or ^{131}I or ^{67}Cu (instant claim 66) for the specific radionuclides as the therapeutic agent.

The '368 patent teaches a method for delivering a conjugate comprising a therapeutic agent and antibodies to selectively kill a specific cell population, such as malignant tumor cells, *in vivo* (see the abstract and column 1, paragraph 2 in particular). The antibody allows for targeting of the conjugate to a specific tumor cell antigen (see column 2, paragraph 2 in particular). The therapeutic agent used can be bleomycin, cyclphosphamide, dacarbazine, daunorubicin, doxorubicin, cluorouracil, mechlorethamine, procarbazine hydrochloride, vinblastine, vincristine, ^{131}I or ^{67}Cu, and other cytotoxic radionuclides (see columns 5-6 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tumor-specific immunotoxins taught by the'368 patent for the tumor-specific immunotoxins taught by the'923 patent and WO 92/00762 for cancer therapy.

One of ordinary skill in the art would have been motivated to substitute the tumor-specific immunotoxins taught by the'368 patent for the tumor-specific immunotoxins taught by the'923 patent and WO 92/00762 because the anti-CD30 antibodies taught by the '923 patent target CD30 on Hodgkin's disease and lymphoma cells, and CD30L could be used as the natural ligand as taught by the WO 92/00762 reference to selectively kill a specific cell population, such as malignant tumor cells, *in vivo* as taught by the '368 patent.

13. Claims 50-53, 54-57, 59, 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63, and 65 above, and further in view of U.S. patent 4,867,962.

The '923 and WO 92/00762 references has been discussed supra.

The combined reference teachings do not teach ^{188}Re, ^{186}Re, ^{212}Pb, ^{212}Bi, ^{109}Pd, ^{64}Cu, ^{67}Cu, ^{131}I, or 2^{11}At as the specific radionuclide (instant claim 66), trichothecene as the mycotoxin (instant claim 64), L-phenylalanine nitrogen mustard (instant claim 51), cyclophosphamide (instant claim 51), cis-diaminodichloroplatinum (instant claim 53), 5-fluorouracil (instant claim 55), vincristine (instant claim 57), bleomycin (instant claim 59) as the specific therapeutic agent.

The '962 patent teaches a method of delivering a therapeutic agent to a desired target site within a human or mammalian host. The agents are attached to an antibody (i.e. a conjugate; see column 1, paragraphs 1 and 3; column 2, lines 45-68 in particular). The '962 patent teaches that any known therapeutic agent may be used (see column 5, lines 32-33 in particular). A few of the agents are ^{188}Re, ^{186}Re, ^{212}Pb, ^{212}Bi, ^{109}Pd, ^{64}Cu, ^{67}Cu, ^{131}I, 2^{11}At, ricin, abrin, diptheria toxin, Pseudomonas exotoxin A, ribosomal inactivating proteins, mycotoxins (e.g. trichothecenes), L-phenylalanine nitrogen mustard, cyclophosphamide, cis-diaminodichloroplatinum, 5-fluorouracil, vincristine, bleomycin (see column 5, paragraphs 1-4 in particular). The method enhances the delivery of therapeutic agents to a cancer site (i.e. a tumor specific site) with a comparatively lower amount of agent delivered to non-target sites results in reduced toxicity toward normal tissues (see column 1, paragraph 1; column 2, lines 67-68 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunotoxin with one of the specific therapeutic agents taught the '962 patent for the immunotoxins taught by the '923 and WO 92/00762 references for effective cancer therapy.

One of ordinary skill in the art would have been motivated to substitute immunotoxin with one of the specific therapeutic agents taught the '962 patent for the immunotoxins taught by the '923 and WO 92/00762 references because the anti-CD30 antibodies taught by the '923 patent target CD30 on Hodgkin's disease and lymphoma cells, and CD30L could be used as the natural ligand as taught by the WO 92/00762 reference to enhance the delivery of therapeutic agents to a cancer site (i.e. a tumor specific site) with a comparatively lower amount of agent delivered to non-target sites results in reduced toxicity toward normal tissues as taught by the '962 patent.

14. Claims 28-30, 32-46, and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,165,923 (IDS reference) in view of WO 92/00762 as applied to claims 27, 38, 50, 58-63, and 65 above, and further in view of WO 93/24135.

The '923 and WO 92/00762 references have been discussed supra.

The combined reference teachings do not specifically teach a CD30L as the natural ligand, CD30L polypeptide having the sequences of SEQ ID NOS: 6, 8, 19, or 23, fragments thereof, oligomers of CD30L, or fusion proteins with IgG1 Fc domain linked to CD30L.

The WO 93/24135 document teaches membrane-bound and soluble CD30L polypeptide having the sequences of SEQ ID NOS: 6, 8, 19, and 23 (see claims 15-16, 18, 19-20 and figures 3a, 5a, 6a, and 7a in particular) which are full-length and soluble fragments of CD30L. The WO 93/24135 document further teaches that the CD30L polypeptide binds to CD30, which is found on Hodgkin's Disease tumor cells and lymphomas (see the Abstract and page 1, paragraph 1 in particular). Further, "CD30L has potential use as a therapeutic agent" (see page 3, lines 29-30 in particular); and "CD30L includes membrane-bound proteins as well as truncated proteins that retain binding capacity, such as extracellular domains (i.e. soluble fragments; see page 4, lines 11-14 in particular). CD30L can be modified to form covalent or aggregate conjugates with other moieties (see page 9, paragraph 3 in particular) and can exist as oligomers, such as dimers and trimers via disulfide bonds or peptide linkers (see page 13, paragraphs 2-3 in particular). The oligomers of CD30L extracellular domains can be expressed as a fusion protein linked to

an IgG Fc region, such as human IgG1 Fc region (see page 13, paragraph 4; and page 37, Example 11 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the soluble CD30L polypeptide having the sequences of SEQ ID NOS: 19 and 23, oligomers, and fusion proteins taught by the WO 93/24135 document for the natural ligand taught by the WO 92/00762 to create an immunotoxin conjugate having a specific binding molecule for CD30 present on the cell surface of Hodgkin's Disease tumor cells and lymphomas as taught by the '923 patent.

One skilled in the art would have been motivated to make an immunotoxin comprising a conjugate of a soluble CD30L extracellular domain with or without a human IgG1 Fc region fusion partner taught by the WO 93/24135 document with a therapeutic agent to target Hodgkin's Disease tumor cells and lymphomas as taught by the '923 patent as taught by the '923 patent and WO 93/24135/ WO 92/00762 documents because normal irradiation is not always completely successful, and the immunotoxins allow for specific targeting of tumor cells with fewer side reactions as taught by the '923 patent.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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April 15, 2002

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